SAMARIUM DIIODIDE IN SYNTHESIS: SYNTHESIS OF THE C-RING OF ANGUIDINE AND THE CONVERSION OF ALDEHYDES AND KETONES INTO 1,2-DIACETATES AND 1,2-DIOLS

BY

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1990

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by

Hikmet Satici

To my Father and Mother.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SAMARIUM DIIODIDE IN SYNTHESIS: SYNTHESIS OF THE C-RING OF ANGUIDINE AND THE CONVERSION OF ALDEHYDES AND KETONES INTO 1,2-DIACETATES AND 1,2-DIOLS

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Chairman: Eric J. Enholm
Major Department: Chemistry

The enantioselective synthesis of the C-ring of anguidine in protected form was achieved from the known (L)-arabinose lactol, 2-O-(t-butyldimethylsilyl)-3,4-O-isopropylidine-(L)-arabinose. A key transformation in this synthetic route involved the diastereoselective samarium diiodide mediated cyclization of a carbohydrate template. The template contained an aldehyde suitably tethered to an activated olefin which produced a highly oxygenated 5-membered carbocycle. The stereochemistry of this cyclization was confirmed by a combination of chemical transformations and nuclear Overhouser effect studies.

The use of samarium diiodide in carbonyl homologation was also investigated. In this study, a variety of aldehydes and ketones was directly transformed into 1,2-diacetates.

This new method utilized samarium diiodide and hexamethylphosphoramide reagent system and bromomethyl acetate in THF at room temperature. The resulting diacetates were hydrolyzed with potassium carbonate in THF-MeOH-H_2O solvent mixture to give 1,2-diols. This is the only known method to accomplish this transformation from commercially available reagents in one step.

CHAPTER 1

INTRODUCTION

Lanthanides are elements which were discovered between 1850 (Ce) and 1945 (Pm). The 15 elements from lantalum to lutetium constitute a unique family of closely related elements differing in the number of 4f electrons. The main uses of lanthanides are in ceramics and glasses as additives and dyes, metallurgy, electronics (magnetic or luminescence materials) and petrochemicals (catalytic cracking or oxidation by lanthanide oxides). Lanthanides are familiar to every organic chemist as NMR shift reagents.[1] Another well known lanthanide-based methodology is found in cerium(IV) oxidations.[2]

The main oxidation state of lanthanides is +3 and several Ln(IV) compounds are powerful oxidants;[3] conversely, divalent lanthanides are reductants or one electron donors.[4] Another characteristic of lanthanides is their strong affinity for oxygen which can be useful for the activation and chelation of oxygenated organic functions.

The dipositive oxidation state is unusual for the lanthanides and is attained only with europium ($Eu^{2+} = 4f^7$), samarium ($Sm^{2+} = 4f^6$), and ytterbium ($Yb^{2+} = 4f^{14}$). In the lanthanide (II) oxidation state, the usual driving force for reactions is electron transfer to give the Ln (III) species.

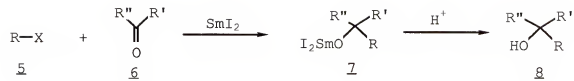
E°_{aq} values (Ln^{3+}/Ln^{2+}) are -0.35V, -1.15V and -1.55V for europium, ytterbium and samarium, respectively.[5] Eu^{2+} salts are quite stable in water, while Sm^{2+} and Yb^{2+} reduce water rapidly. Since samarium (II) has the highest reduction potential, it is the best candidate for the reactions that involve reductions and reductive couplings.

The first use of samarium (II) in organic chemistry came from Girard, Namy and Kagan in 1980, when they prepared samarium diiodide solution in THF, by reacting samarium metal with diiodoethane (Scheme 1) and investigated its reactivity as one electron donor.[6]

1 2 3 4

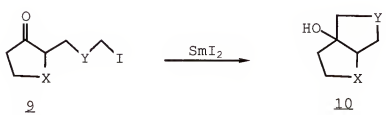
Scheme 1

In their first historical report, they showed that samarium diiodide can be used to couple alkyl halides with aldehydes and ketones in a Barbier-like reaction (Scheme 2). This one-pot reaction is particularly important because of the accessibility of the starting materials, SmI_2 and the stability of its THF solutions when protected from oxygen.



Scheme 2

Later, Molander and Etter used the intramolecular version of this Barbier-like reaction to prepare bicyclic alcohols 10 through the cyclization of 2-(n-haloalkyl) cycloalkanones 9 mediated by SmI_2 (Scheme 3).[7] The mechanism of the Barbier-like reactions has been investigated, and electron transfer reactions with radical intermediates are likely.[8]



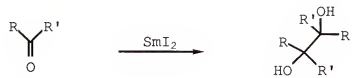
X= $(CH_2)_n$, n= 1,2,3
Y= $(CH_2)_m$, m= 1,2

Yields= 59-85%

Scheme 3

Samarium diiodide is an excellent reagent for pinacol 12 formation from aldehydes and ketones in aprotic THF solutions (Scheme 4). Pinacols from aromatic aldehydes form very rapidly (1-2 min.) at room temperature giving high yields.

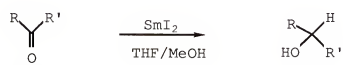
Aliphatic aldehydes form pinacols after a few hours, while aliphatic ketones may require a day.[9,10]



11 12

Scheme 4

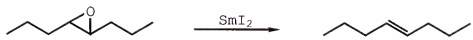
THF solutions of samarium diiodide in the presence of methanol has been shown to reduce aldehydes to corresponding alcohols very efficiently (Scheme 5). Under the same conditions, ketones are reduced much more slowly, allowing the selective reduction of aldehydes.[6,11] In conjugated aldehydes and ketones there is a competition between C=C and C=O reductions.[6]



13 14

Scheme 5

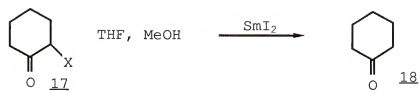
Epoxides can be easily deoxygenated using SmI_2 to corresponding alkenes in excellent yields (Scheme 6).[7]



15 16

Scheme 6

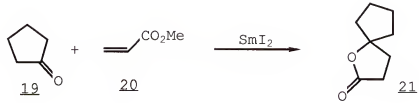
Samarium diiodide is also the reducing agent of choice for the reduction of α-hetero substituted ketones (17) to ketones (18). According to Molander and Hahn reductive eliminations to ketones were achieved when X is OAc, $OSiMe_3$, $OCOCH_2Ph$, OTs, Cl, SPh, SO_2Ph or HgCl shown in Scheme 7.[12]



17 18

Scheme 7

Another very interesting samarium diiodide-mediated reaction was reported by Otsubo, Inanaga and Yamaguchi, where he succeeded in coupling ketones (19) with α-β-unsaturated esters (20) to obtain spiro lactones (21) (Scheme 8).[13]

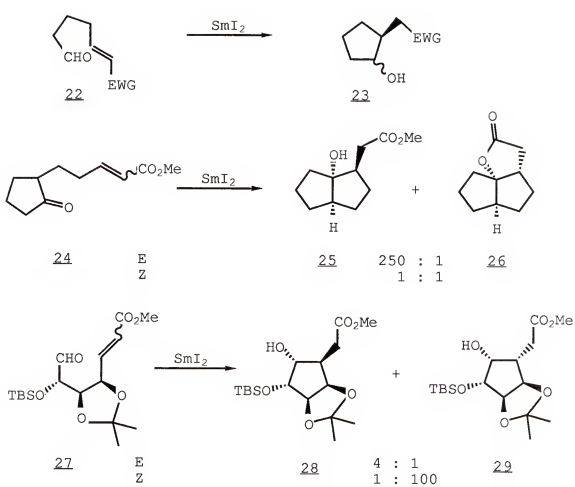


19 20 21

Scheme 8

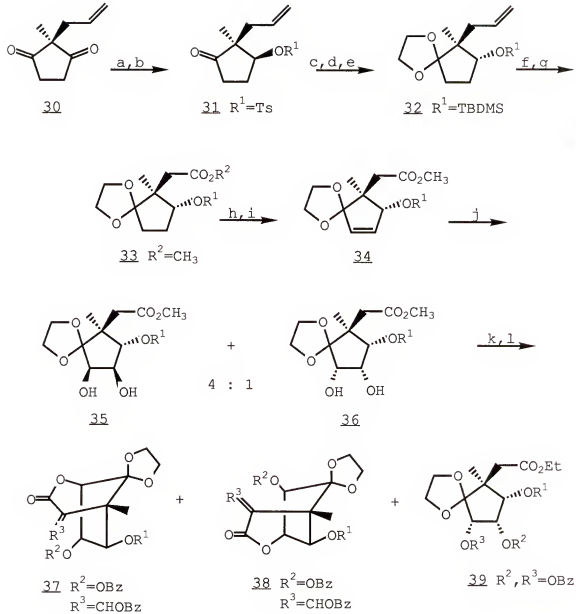
Work of Otsuba et al was particularly intriguing because of its further implications to five membered carbocycle synthesis which is one of the long time interests in our group. Therefore, Enholm and Trivellas undertook the investigation of the intramolecular version of this reaction where an aldehyde or ketone is suitably tethered to an activated olefin. They were rather successful in forming the 5-membered carbocyclic rings.[14,15] During their investigation they also made an important discovery. They found that in a number of cases the stereochemical outcome of the cyclization is dependent on the geometry of the olefin. When E-olefins were used, anti products predominated (up to 250:1 anti/syn). Similarly when Z-olefins were used, syn products were nearly exclusively formed (up to 1:100 anti/syn). Similar results were obtained with modified carbohydrate templates (Scheme 9).

Since an enormous stereoselectivity was achieved in the 5-membered ring synthesis, we decided to apply this cyclization methodology in natural product synthesis.[16] As a target we chose the compound anguidine (40) which contains a highly oxygenated 5-membered ring. Anguidine (40) is a member of the trichothecene family of sesquiterpenes which are a



Scheme 9

class of secondary metabolites produced by various species of *fungi imperfecti*.[17-20] Trichothecenes exhibit a wide range of antifungal, antibacterial, antiviral and other biological activities.[21] Although the trichothecene anguidine is an important anticancer cytopathological agent, it is also a structurally interesting synthetic target, with only one effort by Brooks and co-workers involving the successful use of an enantioselective approach.[22,23] Their approach to the C ring is pictorially displayed in Scheme 10.



30 31 R^1=Ts 32 R^1=TBDMS

33 R^2=CH_3 34

35 36

37 R^2=OBz R^3=CHOBz 38 R^2=OBz R^3=CHOBz 39 R^2,R^3=OBz

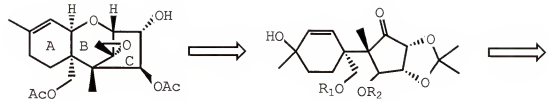
(a) Dry Baker's yeast, pH 7 buffer, D-glucose, 70%. (b) p-Tosyl chloride, pyridine, 85%. (c) DMF, KNO_2, 85° C. (d) DMF, Imidazole TBS-Cl, DMAP. (e) Ethylene glycol, p-TSA, triethyl orthoformate. (f) t-Butanol, H_2O, K_2CO_3, $NaIO_4$, $KMnO_4$, 75%. (g) CH_2N_2, ether. (h) Phenyltrimethylammonium tribromide, THF, 95%. (i) DBU, 90° C (j) Acetone-H_2O, NMO, OsO_4 (k) NaH, ethyl formate, ether. (l) Benzoyl chloride, pyridine.

Scheme 10

CHAPTER 2
RETROSYNTHETIC PLAN

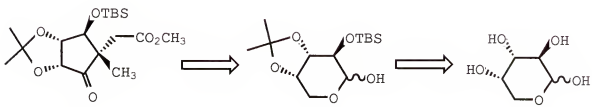
There were several considerations in our assessment of the C ring in anguidine which had to be dealt with in the overall retrosynthetic analysis of this molecule. First the route should be versatile enough with regard to protecting groups and other manipulations to prepare intermediates in the latter stages of the synthesis for biological testing. Secondly, the approach should be flexible enough to permit the synthesis of the other members of the trichothecene family. Finally, the synthesis had to be simpler and/or more efficient than the previous effort.[22,23]

Thus, cyclopentanone (42), which contains all of the necessary oxygenated functionality and stereochemistry for the assembly of anguidine, represents a protected version of the C-ring for these studies. The spiro-epoxide functionality in the C-ring can easily be constructed at a later stage in the synthesis from the precursor ketone moiety, and this has been demonstrated in several previous racemic routes to trichothecenes.[46-49] The key part of our synthetic plan was the recognition that 47, a densely oxygenated cyclopentane could arise from the protected carbohydrate lactol 45 by the samarium diiodide-mediated reductive process outlined in Scheme 12.[15]



40 41

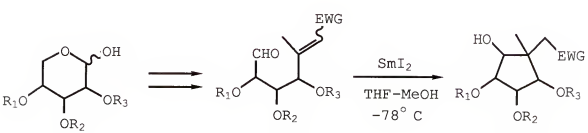
Anguidine



42 43 44

L-arabinose

Scheme 11



45 46 47

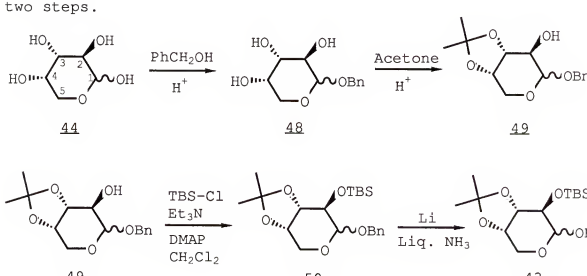
Scheme 12

It must be noted that the carbohydrate lactol 45 must be deoxygenated and a new quaternary sp^3 carbon center in 47 must be established in this sequence.

CHAPTER 3
RESULTS AND DISCUSSION

Synthesis of the C-ring of Anguidine

Our synthesis begins with the preparation of the known lactol (43) from L-arabinose (44).[24] As shown in Scheme 13, this was achieved by first forming the benzyl glycoside of L-arabinose (48) and then protecting the cis-hydroxyl groups as an acetonide (49) (82% for two steps). Protection of the remaining hydroxyl functionality as its t-butyldimethylsilyl ether (50) was followed by dissolving metal reduction with lithium in liquid ammonia which provided the deprotection of benzyl group and gave the known lactol (43), in 61% yield for two steps.



44 48 49

49 50 43

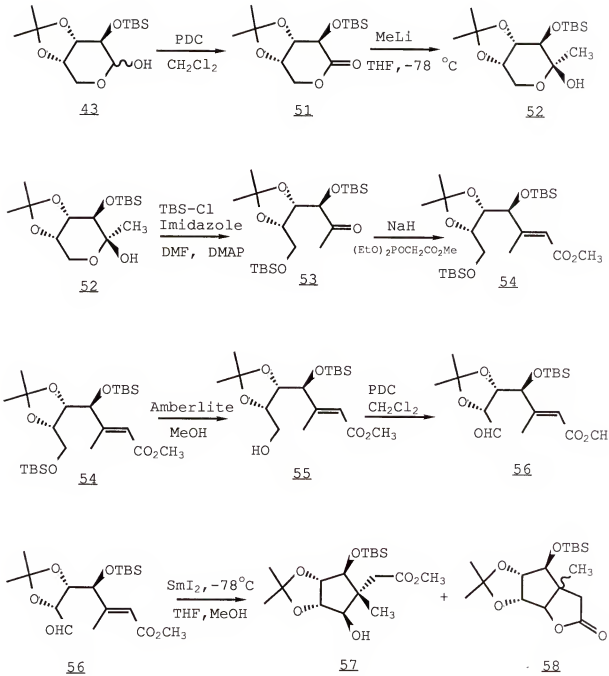
Scheme 13

Lactol (43), which is readily available from L-arabinose in good yield, was oxidized with pyridinium dichromate to give lactone (51) as white crystals in 79% yield (Scheme 14). Treatment of lactone (51) with MeLi at low temperature afforded the hemiketal (52) as a single diastereomer with the stereochemistry depicted for (52). This was confirmed by a difference NOE experiment where irradiation of the methyl group showed a 6% NOE enhancement in the C_2 proton. Although a mixture was anticipated at this step, the endo stereochemistry probably reflects the steric requirements for the attack of the methyl nucleophile and avoidance of the adjacent bulky t-butyldimethylsiloxy functionality. A quite different thermodynmic argument for the stereochemistry of the hemiketal (52) arises from the anomeric effect. It is possible that the hemiketal stereochemistry with the endo-disposed methyl is the thermodynamically most stable product and a result of equilibration through the acyclic keto-alcohol form. The major side product of this reaction was found to be the double addition product and was minimized by using 1.4 equivalent of MeLi and very dilute reaction medium (0.05M) at -78 °C yielding 68% of the desired hemiketal (52).

The single diastereomer obtained for hemiketal (52) was actually inconsequential because a subsequent treatment with t-butyldimethylsilyl chloride, under very mild conditions, produced the acyclic ketone (53) in 97% yield. Next, an Emmons-Wittig reaction with the sodium salt of methyl

diethylphosphonoacetate rendered the exclusive E-geometric isomer for the α,β-unsaturated ester (54) in 90% yield. This was confirmed by difference NOE studies in which irradiation of the sole olefin proton caused a 6.6% enhancement of the C_2 proton. The Z-isomer could not be observed by either ^1H NMR or chromatographic methods. The subsequent removal of the sterically most accessible t-butyldimethylsilyl group was not easily accomplished. Various fluoride ion-based deprotection methods resulted in partial or complete decomposition of the starting material. Boron trifluoride etherate methodology selectively released the wrong C_2 hydroxyl group. Finally, desired selective deprotection was achieved by stirring compound (54) with Amberlite acidic ion exchange resin in methanol to produce compound (55). This deprotection could also be achieved by acetic acid-THF-water hydrolysis method but Amberlite method was preferred because of its higher isolated yield (60%) and shorter reaction time (16 hours). An uneventful oxidation of the resulting primary alcohol (55) to an aldehyde led to the preparation of the modified carbohydrate template (56) in 96% yield.

The E-geometric isomer for the carbohydrate template (56) was a prerequisite for anticipated success of the key cyclization reaction mediated by samarium diiodide. This is due to the correlation between the starting olefin geometry and the product diastereoselectivity, where we expected the anti diastereomer to prevail from the E-olefin (Scheme 9). It should be noted that a more direct means of constructing



Scheme 14

carbohydrate template (56) can be envisioned as arising from a direct Wittig with hemiketal (52), which would apparently

eliminate the protection-deprotection sequence realized above. However, this reaction in our hands was unsuccessful. In addition, previous experience in our group with Wittig reactions of arabinose lactols with stabilized ylids produced Z-isomer as major product. Similar results with furanose lactols have been observed by Webb et al.[25] It appears that C_5 hydroxyl functionality in the acyclic form of the lactol plays an unclear role in the formation or decomposition of the oxaphosphatene and leads to a predominance of the Z-isomer. Blocking the C_5 hydroxyl group as its t-butyldimethylsilyl ether and locking the hemiketal in its acyclic ketone form (53) insures the E-product will predominate in the Emmons-Wittig reaction.

Thus, treatment of (56) with samarium diiodide in THF at -78 °C in the presence of methanol as a proton donor produced the highly oxygenated cyclopentane (57) and a minor lactone product (58) in a ca. 5:1 ratio, respectively, as shown in Scheme 14. The major product (57) could be easily isolated in 65% yield. Finally, oxidation of the sole ring hydroxyl functionality of compound (57) with pyridinium dichromate gave the ketone (42) in 81% yield, completing the synthesis of the protected C-ring of anguidine (Scheme 15).

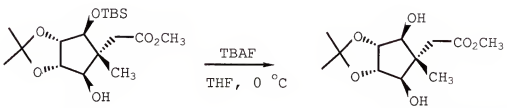
57 42

C-ring of anguidine

Scheme 15

Confirmation of the Stereochemistry of the Cyclized Product

The stereochemistry of the cyclized product (57) was confirmed by deprotecting the t-butyldimethylsiloxyl moiety with fluoride ion (Scheme 16). A plane of symmetry was clearly apparent in the syn-diol product (59), as was evidenced by the simple ^{1}H NMR and ^{13}C NMR spectra.

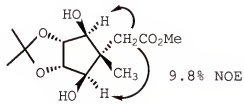


57 59 "Symmetric"

Scheme 16

Additional confirmation of the stereochemistry of the key cyclization was obtained from difference NOE experiments performed on the syn-diol (59). Irradiation of the methylene protons on the ester appendage gave a 9.8% enhancement of the

two equivalent protons on the hydroxy-bearing ring carbons. Similarly, irradiation of the methyl protons produced a 7.9% NOE enhancement of the two equivalent protons on the acetonide-bearing ring carbons (Figure 1).



59

Figure 1

Thus, a combination of chemical and spectroscopic methods unequivocally confirmed the stereochemistry of the cyclized product (57).

Experimental for the Synthesis of the C-ring of Anguidine

General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Varian VXR-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on a Varian VXR-300 spectrometer. Chemical shifts are reported in ppm downfield

relative to tetramethylsilane (CH_4Si) as an internal standard in $CDCl_3$. Exact mass measurements were performed on an AEI M530 mass spectrometer. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA 30091.

All reactions were run under an inert atmosphere of nitrogen or argon using flame dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography and NMR spectroscopy. Temperatures below ambient temperature refer to bath temperatures unless otherwise stated. Solvents and anhydrous reagents were dried according to established procedures by distillation under nitrogen from an appropriate drying agent: ether and THF from benzophenone ketyl; chloroform and ethyl acetate from CaH_2.

Analytical TLC was performed using E. Merck precoated silica gel plates (0.25 mm) using phosphomolybdic acid in ethanol as an indicator. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh) by standard flash chromatographic techniques.

2-O-(t-butyldimethylsilyl)-3,4-O-isopropylidine-(L)-arabinose (43)

To a suspension of L-arabinose (15 g; 0.10 mol) in 60 ml benzyl alcohol, was added 1.1 g of toluenesulfonic acid. The resulting mixture was kept warm at 60-90 °C. After 0.5h, the solution was complete and the contents of the reaction flask

were poured into an ice cold mixture of 700 ml hexanes and 350 ml of ether. White crystals which formed immediately were isolated by suction filtration. After being dried in a 500 ml flask overnight with a vacuum pump, the resulting hygroscopic white crystals (48) were used without further purification in the next step.

The crystals were next placed in a 500 ml flask with acetone (150 ml), 2,2-dimethoxpropane (50 ml) and toluenesulfonic acid (0.5 g) at room temperature. After stirring 2 h, the reaction was quenched with aq. sat. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. Purification by suction chromatography gave 22.86 g (82% for two steps) of the desired acetonide (49).

Compound (49) (7.0 g; 25 mmol) was dissolved in CH_2Cl_2 (25 ml). To this solution was added Et_3N (13.9 ml; 100.0 mmol), DMAP (610 mg), and t-butyldimethylsilyl chloride (7.5 g; 50 mmol). After stirring for 12 h, the reaction was quenched with aq. sat. $NaHCO_3$ and extracted with ether. The combined organic layers were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. Crude reaction products were transferred into a 3-necked flask and were dissolved in THF (60 ml). Into this solution NH_3 (180 ml) was condensed at -78 °C and small pieces of sodium metal were added until the solution color became dark blue. The solution was kept at this color for 8.5 minutes and then carefully quenched with

diiodoethane-THF (1:1, v:v) solution, followed by solid ammonium chloride. Ammonia was evaporated by passing N_2 gas through the flask and then water was added to the resulting slurry. Extraction with ethyl acetate was followed by drying the organic layers over anhydr. Na_2SO_4 and concentrating under reduced pressure. Purification by chromatography yielded 4.6 g (61% for two steps) of the lactol (43).

2-O-(t-butyldimethylsilyl)-3,4-O-isopropylidine-(L)-arabinolactone (51)

A mixture of lactol (43) (1.31 g; 4.31 mmol), Pyridinium dichromate (3.50 g; 9.31 mmol), acetic acid (100 µl) and molecular sieves (3.5 g) in CH_2Cl_2 (17 mL) was stirred for 24 h at room temperature. Water was added, and the mixture was extracted with ether. The combined ether layers were dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography gave 675 mg (52%) of the title compound (51) and 360mg (27%) of the starting material was recovered

R_f 0.50 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.29-4.75 (m, 5 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 0.9 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 168.5, 110.4, 76.4, 71.4, 70.4, 67.4, 26.0, 25.5, 24.1, 18.0, -5.2, -5.4; IR (KBr) 2935, 1756, 1384, 1267, 1211 cm^{-1}. Anal. Calcd: C, 55.60; H, 8.67. Found: C, 55.45; H, 8.86.

Hemiketal (52)

Lactone (51) (254 mg; 0.841 mmol) was dissolved in THF (16.8 mL). To this solution at -78 °C, MeLi (84 μL, 1.4 M in THF, 1.177 mmol) was added via syringe, and the solution was slowly allowed to warm up to room temperature. The reaction was then quenched with aq. sat. NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4. Concentration under reduced pressure followed by flash chromatography gave 180.6 mg (68%) of hemiketal (52) as white crystals.

R_f 0.35 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 3.84-4.21 (m, 4 H), 3.6 (d, J = 6 Hz, 1 H), 3.10 (s, 1 H), 1.52 (s, 3 H), 1.42 (s, 3H), 1.35 (s, 3 H), 0.92 (s, 9 H), 0.18 (s, 3 H), 0.13 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 109.1, 96.4, 76.6, 74.6, 73.2, 60.0, 27.7, 26.8, 26.0, 25.8, 18.0, -4.2, -5.2; IR (KBr) 3398, 2900, 1250, 1200, 1100, 1045 cm^{-1}. Anal. Calcd: C, 56.57; H, 9.49. Found: C, 56.59; H, 9.63.

3-(R)-(t-butyldimethylsiloxy)-4-(S),5-(R)-O-isopropylidine-6-t-butyldimethylsiloxy-2-hexanone (53)

A solution containing hemiketal (52) (280 mg; 0.88 mmol) in DMF (3.6 ml) was treated with imidazole (300 mg; 4.40 mmol), DMAP (11 mg; 0.09 mmol) and t-butyldimethylsilyl chloride (397 mg; 2.64 mmol) at room temperature. After

being stirred overnight, water was added, and the mixture was extracted with ether. The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography yielded 369 mg (98%) of the title compound (53) as a clear oil.

R_f 0.50 (10% ether hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.18-4.38 (m, 3 H), 3.61-3.79 (m, 2 H), 2.21 (s, 3 H), 1.48 (s, 3 H), 1.35 (s, 3 H), 0.95 (s, 9 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 207, 108, 77.9, 77.5, 77.2, 62.5, 27.5, 27.1, 25.9, 25.8, 25.1, 18.5, 18.2, -4.2, -4.5, -5.3; IR (neat) 2930, 1721, 1473, 1254, 1217, 1098, 839 cm^{-1}. Anal. Calcd: C, 58.29; H, 10.25. Found: C, 58.41; H, 10.27.

α,b-Unsaturated ester (54)

NaH (106.4 mg; 0.86 mmol; 60% oil dispersion) was washed with n-pentane (3x5 mL) and then diluted with THF (1.7 mL). To this suspension at room temperature, methyl diethylphosphonoacetate (483 μL, 2.57 mmol) was added via syringe. After the gas evolution was complete, acyclic ketone (53) (369 mg; # mmol) in 0.9 mL THF was added to this solution via syringe. After stirring 12 h the reaction was quenched with water and extracted with ether. The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column

chromatography gave 377 mg (90%) of the title compound (54) as a clear oil.

R_f 0.33 (10% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 5.85 (s, 1 H), 4.35 (d, J = 7 Hz, 1 H), 4.02-4.20 (m, 2 H), 3.66-3.84 (m, 2 H), 3.65 (s, 3 H), 2.15 (s, 3 H), 1.48 (s, 3 H), 1.32 (s, 3 H), 0.90 (s, 18 H), 0.08 (s, 3 H), 0.04 (s, 6 H), 0.00 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 167.1, 158.5, 117.9, 108.5, 79.1, 78.0, 76.5, 62.0, 51.0, 27.1, 26.0, 25.8, 18.0, 15.5, -4.2, -4.8, -5.4; IR (neat) 2930, 1725, 1654, 1254, 837 cm^{-1}. Anal. Calcd: C, 58.97; H, 9.90. Found: C, 59.12; H, 9.92.

Alcohol (55)

Alcohol (54) (376 mg; 0.77 mmol) and Amberlite (1.9 g; IR-120 H C.P.) medium porosity ion exchange resin were stirred in methanol (15.5 ml). After 8 hours amberlite beads were removed by quick filtration through a fritted glass, and fresh Amberlite (1.9 g) was added to the filtrate. After stirring for another 8 h the beads were removed by filtration, and the filtrate was concentrated under reduced pressure. Purification by column chromatography yielded 173 mg (60%) of the title compound (55) as an oil.

R_f 0.20 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 5.82 (s, 1 H), 4.02-4.25 (m, 3 H), 3.70 (s, 3 H), 3.60 (m, 2 H), 2.18 (s, 3 H), 1.48 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9

H), 0.08 (s, 3 H), 0.02 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 166.6, 156.8, 118.2, 108.3, 78.9, 77.2, 76.2, 61.3, 51.1, 27.7, 25.7, 25.2, 18.2, 14.8, -4.7, -4.8; IR (neat) 3500 (br), 2932, 1725, 1651, 1253, 839 cm^{-1}. Exact mass calculated for $C_{17}H_{31}O_6$ (M-CH_3) 359.1889, found 359.1898.

Aldehyde (56)

Alcohol (55) (104 mg, 0.278 mmol) was dissolved in CH_2Cl_2 (5.6 ml). To this solution pyridinium dichromate (418 mg; 1.112 mmol), glacial acetic acid (20 μl), and finely ground molecular sieves (1 g) were added. The reaction was complete in less then 45 min. The reaction mixture was diluted with 50% ether/hexanes (15 ml) and was filtered through a pad of silica gel. Concentration under reduced pressure followed by suction chromatography gave 100 mg (96%) of the title compound (56).

R_f 0.48 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 5.85 (s, 1 H), 4.35 (m, 2 H), 4.12 (m, 1 H), 3.68 (s, 3 H), 2.15 (s, 3H), 1.58 (s, 3 H), 1.35 (s, 3 H), 0.90 (s, 9 H), 0.00 (s, 3 H), -0.05 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 200.9, 166.7, 157.3, 118.0, 111.0, 81.9, 80.8, 74.8, 51.1, 26.6, 25.8, 25.1, 18.0, 15.9, -4.0, -5.2; IR (neat) 2932, 1801, 1725, 1659, 1256, 1218 cm^{-1}.

Cyclopentane (57)

To a SmI_2 (19.4 mL; 0.1 M; 1.940 mmol) solution at -23 °C was added the carbohydrate template (56) (180 mg, 0.484 mmol) dissolved in THF (1.0 ml) and MeOH (333 μL) mixture via syringe. After the solution color became yellow-green (approx. 0.5 h), the reaction was quenched with aq. sat. NH_4Cl solution and was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography yielded 118 mg (65%) of the title compound (57).

R_f 0.40 (50% ether hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.48 (2d, 1 H), 4.35 (2d, 1 H), 3.98 (2d, 1 H), 3.85 (d, J = 3.5 Hz, 1 H), 3.70 (s, 3 H), 3.65 (d, J = 6 Hz, 1 H), 2.45 (dd, J_{AB} = 15 Hz, 2 H), 1.48 (s, 3 H), 1.29 (s, 3 H), 0.93 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 174.1, 113.0, 84.0, 83.7, 82.5, 80.8, 51.9, 49.3, 43.5, 26.9, 25.8, 24.8, 17.9, 13.5, -4.4, -5.4; IR (neat) 3470 (br), 2930, 1732, 1258, 1209, 1078 cm^{-1}. Anal. Calcd: C, 57.72; H, 9.15. Found: C, 57.63; H, 9.20.

Ketone (42)

The cyclopentane (57) (33.9 g; 0.091 mmol) was dissolved in CH_2Cl_2 (910 μL). To this solution, pyridinium dichromate

(102.2 mg; 0.271 mmol), glacial acetic acid (10 μl), and finely ground molecular sieves (0.5 g) were added. After 1 h of stirring at room temperature, the reaction mixture was diluted with 10 mL CH_2Cl_2 and filtered through a silica gel pad. Concentration, followed by column chromatography rendered 27.4 mg (81%) of the title compound (42).

R_f 0.56 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.65 (d, 7 Hz, 1 H), 4.55 (t, J = 3 Hz, 1 H), 4.52 (t, J = 3 Hz, 1 H), 2.57 (dd, J_{AB} = 16 Hz, 2 H), 1.51 (s, 3 H), 1.35 (s, 3 H), 1.08 (s, 3 H), 0.91 (s, 9 H), 0.19 (s, 3 H), 0.10 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 212.7, 170.8, 113.6, 82.7, 78.6, 77.0, 53.5, 51.6, 38.6, 26.6, 25.7, 25.1, 18.0, 18.0, -4.7, -5.2; IR (neat) 2933, 1765, 1741, 1254, 1094 cm^{-1}. Exact mass calculated for $C_{14}H_{23}O_6Si$ 315.1264m found 315.1267.

Symmetric diol (59)

A solution of cyclized product (57) (28.7 mg; 0.077 mmol) in THF (308 μL) was treated with a 1M solution of tetrabutylammonium fluoride (154 μL; 0.154 mmol) at room temperature. After 10 min. water (10 ml) was added to the reaction mixture and it was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. Concentration under reduced pressure followed by chromatography yielded 10.7 mg (53%) of the desired compound (59).

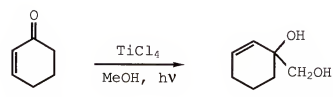
300-MHz ^{1}H NMR ($CDCl_3$) δ 4.40 (d, 3 Hz, 2 H), 3.78 (d, J = 3 Hz, 2 H), 3.63 (s, 3 H), 3.30 (broad, 2 H), 2.50 (s, 2 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 0.90 (s, 3 H); Irradiation of CH_3 group at 0.90 ppm gives 7.9% difference NOE enhancement at 4.40 ppm. Irradiation of CH_2 group at 2.50 ppm gives 9.8% difference NOE enhancement at 3.78 ppm; 75-MHz ^{13}C NMR ($CDCl_3$) δ 174.2, 113.5, 83.7, 81.6, 52.0, 48.8, 43.7, 26.9, 24.6, 12.8; IR (neat) 3500 (br), 2986, 1713, 1208, 1057. Exact mass calculated for $C_{11}H_{17}O_6$ (M-CH_3) 245.1025, found 245.1015.

CHAPTER 4

CONVERSION OF ALDEHYDES AND KETONES INTO 1,2-DIACETATES AND 1,2-DIOLS

Organic chemists have been trying to develop ways to introduce a hydroxymethylene synthon to carbonyl compounds for the last two decades. During this time period, only a few approaches have been successful in obtaining 1,2-diols from aldehydes and ketones.

Direct hydroxymethylation of unsaturated ketones was achieved by Sato in the titanium tetrachloride catalyzed photoreaction of ketones with methanol (Scheme 17).[26] This method is limited to unsaturated ketones and, unfortunately, gives low to moderate yields (35-68%).

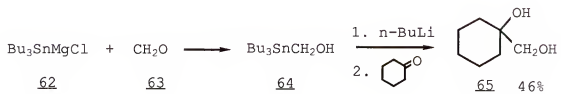


60 61

Scheme 17

Since the direct generation of methanol dianion by a base is not a feasible process, an alternative method was devised by Seebach where he treated Bu_3SnCH_2OH with n-butyllithium to generate a dianion hydroxymethylating reagent

which reacted with aldehydes and ketones, giving 1,2-diols in low to moderate yields (41-65%) (Scheme 18).[27-29]



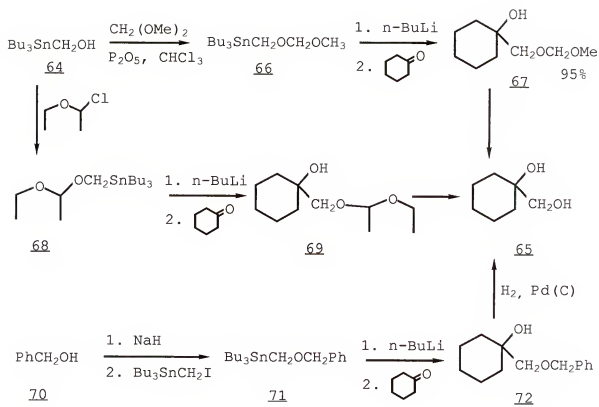
62 63 64 65 46%

Scheme 18

Seebach's method suffers from the difficulties of the preparation of Bu_3SnCH_2OH, the instability of Bu_3SnCH_2OH and the moderate yields of addition products.

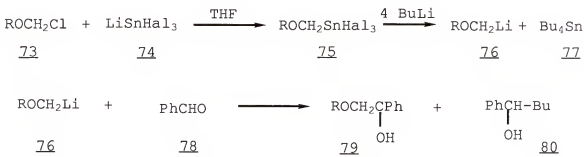
Still extended the utility of Bu_3SnCH_2OH by preparing its ethoxyethyl and benzyl ethers (Scheme 3).[30] Later, Johnson and Medich prepared methoxymethyl protected tributyltin methanol (Scheme 19).[31]

Although the free hydroxyl protected Bu_3SnCH_2OH compounds are quite stable and their addition to carbonyls produces high yields, they add two additional steps to the overall sequence. Also, a deprotection step brings further limitations to the types of substrates that can be used. Deprotection of the ethoxyethyl or methoxymethyl ethers requires strong acid (pKa=1) hydrolysis and deprotection of the benzyl ethers requires harsh hydrogenation or dissolving metal reduction.[32]



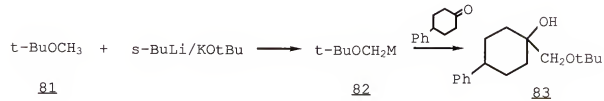
Scheme 19

Corey and Eckcich used protected trihalotin methanol instead of protected tributyltin methanol as hydroxymethylating reagent (Scheme 20)[33] He obtained similar results to those that were obtained by Still and Johnson.



Scheme 20

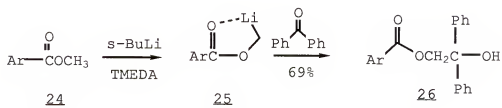
Corey and Eckrich also achieved the direct preparation of t-butoxymethyllithium from t-butyl methyl ether with s-BuLi/KOtBu combination. He successfully reacted this hydroxymethyl anion equivalent with aldehydes and ketones to give mono-t-butyl protected 1,2-diols (Scheme 21).[34]



81 82 83

Scheme 21

Metallation of methyl esters of aryl carboxylic acids by sec-butyllithium-tetramethylethylenediamine and their addition to the carbonyls give mono-protected-1,2-diols which release 1,2-diols upon subsequent $LiAlH_4$ reduction (Scheme 22).[35]

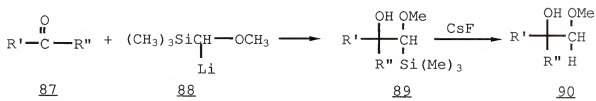


24 25 26

Scheme 22

Another hydroxymethylation method was developed by Magnus. It involves the addition of lithium methoxy(trimethylsilyl)methylide to carbonyls followed by the

removal of TMS group by fluoride ion. Subsequent deprotection of methyl ether is also necessary in order to obtain 1,2-diols (Scheme 23).[36] This method is very lengthy and applicable to limited substrates because of the reagents involved in the sequence. Morover, replacement of the methoxy substituent with hydroxyl poses severe problems with this methodology.

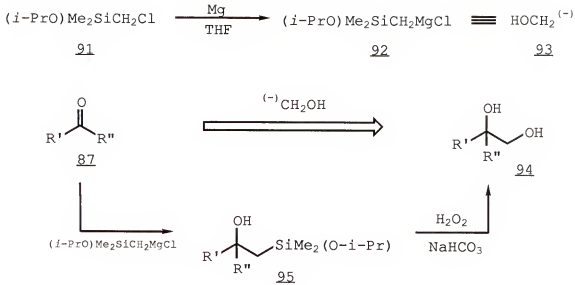


87 88 89 90

Scheme 23

A quite different approach for the hydroxymethylation of aldehydes and ketones came from Tamao and Ishida. In their method, they used (isopropoxydimethylsilyl)methyl Grignard reagent as a hydroxymethyl anion equivalent in conjunction with the oxidative cleavage of the silicon-carbon bond in the Grignard addition product by hydrogen peroxide as shown in Scheme 24.[37]

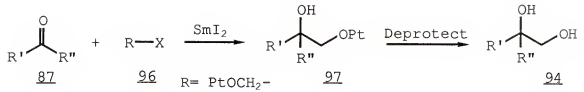
Tamao's method suffers from the instability of the Grignard reagent and the substrate limitations of the oxidative cleavage step.



Scheme 24

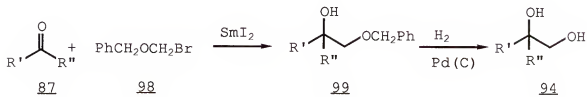
In addition to their individual limitations, all of the above methods (except the photochemical method) require highly basic reaction conditions which also put additional restrictions on the carbonyl substrate that can be used. Therefore, there is a need for new methods which grant milder reaction conditions and offer more versatility in terms of the carbonyl substrates.

Samarium diiodide, a popular one-electron reducing agent is known to alkylate aldehydes and ketones in a Barbier-like reaction (Scheme 25).[35] We realized that if the R group in Scheme 25 is modified as Pt-OCH_2-, where Pt is a suitable protecting group, the addition products to carbonyls would be mono-protected 1,2-diols which should release 1,2-diols upon deprotection (Scheme 9). This would achieve a mild hydroxymethylation.



Scheme 25

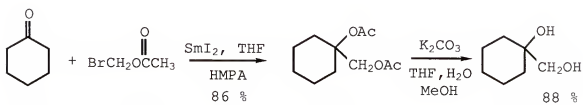
In the literature we found only one example of this approach with samarium diiodide where the alkyl halide is bromomethyl benzyl ether (Scheme 26).[38]



Scheme 26

Although this example by Imamoto works successfully with aldehydes and ketones, it is limited because of the deprotection methods required for the benzyl ethers (hydrogenation or dissolving metal reduction) and bromomethyl benzyl ether is toxic and unstable. Therefore, we searched for another alkyl halide which is commercially available and easier to deprotect. Bromomethyl acetate seemed like an ideal candidate for this purpose. It is commercially available, and the acetates are very easy to hydrolyse under mildly basic conditions.

Our investigation started with cyclohexanone as the carbonyl substrate. When we addded cyclohexanone (1.0 eq.) and bromomethyl acetate (2.0 eq.) to samarium diiodide solution (4.0 eq.) we isolated only pinacol (cyclohexanone dimer) product after workup. Increasing the amounts of bromomethyl acetate and samarium diiodide did not prevent the pinacol formation (Scheme 27). However, addition of a stoichiometric amount of HMPA (HMPA and a few other complexing agents are known to reduce pinacol formation)[6] to the samarium diiodide solution (6.0 eq. initially) prior to addition of bromomethyl acetate (5.0 eq.) and cyclohexanone (1.0 eq.), produced the methanol diacetate 101 in 86% yield. This product arose from the further acetylation of the initial addition product by excess bromomethyl acetate present in the reaction medium (Scheme 27).



Scheme 27

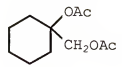
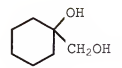
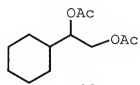
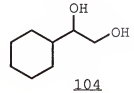
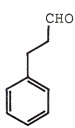
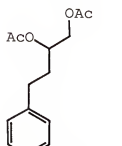
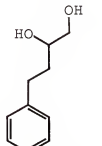
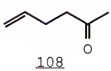
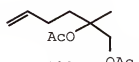
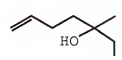
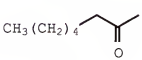
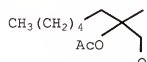
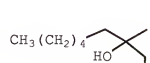
Under the same reaction conditions similar successful results were obtained from variety of aldehydes and ketones and these are tabulated in Table 1. All of these reactions took place under mild reaction conditions and gave high yields. Another important aspect of this reaction is that

this is the only direct way of transforming aldehydes or ketones into 1,2-diacetates. When the same reaction conditions were applied to benzaldehyde or acetophenone, only pinacol products were obtained. In the case of benzaldehyde, diacetylated pinacol product was isolated.

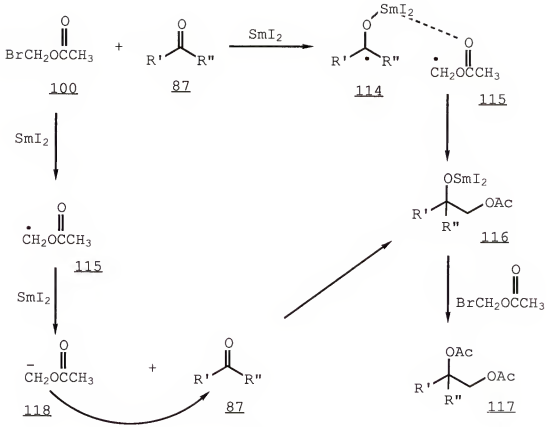
The mechanism of this reaction is believed to be the combination of both radical and anionic processes. In the first process, donation of one electron to both cyclohexanone and bromomethyl acetate by samarium diiodide would produce ketyl and acetoxymethyl radicals respectively. Combination of these radicals followed by acetylation of the intermediate formed can produce the observed 1,2-diacetate. Second process involves the formation of a Grignard type intermediate from two electron addition to bromomethyl acetate. Addition of this intermediate to cyclohexanone followed by acetylation of the addition product can produce the diacetate (Scheme 28). Observation of small amounts of pinacol products in these reactions suggests that ketyl radicals were involved.

When we turned our attention to the hydrolysis of 1,2-diacetates to give 1,2-diols, we found that stirring them with K_2CO_3 in THF-MeOH-H_2O for 24-36 h worked very efficiently and gave the desired 1,2-diols in high yields (Table 1). For the isolation of 1,2-diols, direct column chromatography of

TABLE 1

ENTRY	SUBSTRATE	PRODUCT	YIELD	1,2-DIOLS	YIELD
1	18	 101	86 %	 65	88 %
2	102	 103	88 %	 104	84 %
3	 105	 106	75 %	 107	97 %
4	 108	 109	68 %	 110	96 %
5	 111	 112	86 %	 113	90 %

the reaction mixtures were employed. Because of the water solubility of diols, aqueous workups were avoided. In the case of cyclohexanone when aqueous workup was employed, the isolated yield for the hydrolysis step decreased to 38%.


BrCH2OCCH3
100
87
SmI2
114
115
116
117
118
OSmI2
OAc
R'
R"
CH2OCCH3

Scheme 28

Experimental for 1,2-Diacetates and 1,2-Diols

General procedure for the preparation of 1,2-diacetates

SmI_2 (30 ml, 0.1M in THF, 3.0 mmol) was placed in a 100 ml round bottom flask under argon. HMPA (521 µl, 3.0 mmol), bromomethyl acetate (245 µl, 2.5 mmol) and an aldehyde or a ketone (0.5 mmol) were drawn into three separate syringes in order to provide a fast addition. First, HMPA was added. Immediately after the solution color turned purple (Less than 1 min.), bromomethyl acetate and the carbonyl substrate were added quickly, in this order. Solution color became yellowish green after 5-10 minutes. Then, more SmI_2 solution (10 ml, 0.1M in THF, 1.0 mmol) was added and the reaction mixture was allowed to stir for 10 min. at room temperature. This was followed by the addition of another 10 ml of SmI_2 (0.1M in THF, 1.0 mmol) solution. The resulting reaction mixture was stirred for 8-10 h and was quenched with aq. sat. NH_4Cl solution. Ethyl acetate and water were added and the mixture was stirred for 1 hour. The solution was extracted with ethyl acetate and the combined organic layers were dried over anhydr. Na_2SO_4 and were concentrated under reduced pressure. Purification by column chromatography gave the 1,2-diacetates in 68-88% yields.

General procedure for 1,2-diacetates to 1,2-diols

Diacetate (0.25 mmol) was treated with $K_2CO_3.1.5H_2O$ (200 mg, 1.21 mmol), in a mixture of THF (0.5 ml), MeOH (0.1) and H_2O (0.1 ml) at room temperature. After stirring for 24-36 h the reaction mixture was directly poured on a silica gel column and flash chromatography was performed which gave the desired 1,2-diols in 84-96% yields.

(1-Hydroxycyclohexyl)methanol diacetate (101)[39]

R_f 0.5 (50% ether-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.35 (s, 2H), 2.08 (s, 3H), 2.03 (s, 3H), 0.95-1.75 (m, 10H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.9, 170.2, 81.5, 66.4, 32.0, 25.1, 22.0, 21.5, 21.0; IR (neat): 2934, 1738, 1368, 1230, 1045 cm^{-1}.

(1-Hydroxycyclohexyl)methanol (65)[28]

300-MHz ^1H NMR ($CDCl_3$) δ 3.45 (s, 2H), 2.60 (br, 1H), 2.40 (br, 1H), 0.9-1.88 (m, 10H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 71.8, 70.1, 34.0, 25.9, 21.8.

1-Cyclohexyl-1,2-ethanediol diacetate (103)

300-MHz ^1H NMR ($CDCl_3$) δ 4.90 (m, 1H), 4,30 (2d, 1H), 4.05 (2d, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 0.8-1.8 (m, 11H);

75-MHz ^{13}C NMR ($CDCl_3$) δ 170.8, 170.6, 75.1, 63.7, 38.7, 29.6, 28.7, 28.2, 26.1, 25.8, 20.8, 20.4; IR (neat): 2928, 1746, 1370, 1228, 1045 cm^{-1}; Exact mass calculated for $C_{12}H_{21}O_4$ (M+1) 229.1440, found (GC-CI, CH_4) 229.1451.

1-Cyclohexyl-1,2-ethanediol (104)[40]

300-MHz ^1H NMR ($CDCl_3$) δ 3.35-3.80 (m, 2H), 2.25 (br, 2H), 0.75-1.90 (m,11H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 76.5, 64.8, 40.7, 29.7, 28.6, 26.3, 26.0.

4-Phenyl-1,2-butanediol diacetate (106)

300-MHz ^1H NMR ($CDCl_3$) δ 7.25 (m, 5H), 5.10 (m, 1H), 4.25 (2d, 1H), 4.08 (2d, 1H), 2.65 (m,2H), 2.08 (s, 6H), 1.90 (m, 2H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.6, 170.4, 140.9, 128.5, 128.3, 126.1, 71.2, 65.0, 32.4, 31.5, 21.7, 21.5. Exact mass calculated for $C_{14}H_{19}O_4$ (M+1) 251.1283, found (GC-CI, CH_4) 251.1285.

4-Phenyl-1,2-butanediol (107)[38]

300-MHz ^1H NMR ($CDCl_3$) δ 7.25 (m, 5H), 3.70 (m, 2H), 3.44 (2d, 1H), 2.78 (m, 2H), 2.02 (br, 2H), 1.80 (m, 2H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 141.8, 128.5, 128.4, 126.0, 71.5, 66.8, 34.7, 31.8.

2-Methyl-5-hexene-1,2-diol diacetate (109)

300-MHz ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.00 (dd, 2H), 4.32 (s, 2H), 2.10 (s, 3H), 2.03 (s, 3H), 1.6-2.0 (m, 4H), 1.5 (s, 3H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.6, 170.2, 137.8, 114.8, 81.7, 67.1, 35.1, 27.6, 22.1, 21.3, 20.8; IR (neat) 2927, 1742, 1642, 1232, 1048 cm^{-1}; Exact mass calculated for $C_9H_{115}O_2$ (M-OAc) 155.1072, found (GC-CI, CH_4) 155.1075.

2-Methyl-5-hexene-1,2-diol (110)

300-MHz ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.02 (dd, 2H), 3.45 (apparent quartet, 2H), 2.35 (br, 2H), 2.15 (m,2H), 1.60 (m, 2H), 1.20 (s, 3H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.2, 114.0, 72.1, 69.8, 37.6, 29.7, 28.1; Exact mass calculated for $C_6H_{11}O$ ($M-CH_2OH$) 99.0809, found (GC-CI, CH_4) 99.0803.

2-Methyl-1,2-octanediol diacetate (112)

300-MHz ^{1}H NMR ($CDCl_3$) δ 4.29 (apparent quartet, 2H), 2.09 (s, 3H), 2.00 (s, 3H), 0.8-1.90 (m, 16H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.6, 170.2, 82.1, 67.2, 35.7, 31.6, 29.4, 23.2, 22.5, 22.1, 21.3, 20.8, 13.9; IR (neat) 2930, 1742, 1368, 1234, 1046 cm^{-1}; Exact mass calculated for $C_{11}H_{21}O_2$ (M-OAc) 185.1542, found (GC-CI, CH_4) 185.1536.

2-Methyl-1,2-octanediol (113)[37]

300-MHz ^{1}H NMR ($CDCl_3$) δ 3.42 (apparent quartet, 2H), 2.30 (br, 2H), 0.8-157 (m, 16H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 73.1, 69.8, 38.8, 31.8, 29.9, 23.7,23.2, 22.6, 14.1.

CHAPTER 5

SUMMARY AND CONCLUSIONS

In conclusion, an efficient, enantioselective synthesis of the C ring of anguidine (42) has been accomplished in 12 steps from commercially available L-arabinose (44). The key transformation involved the one-electron reductant samarium diiodide in the transformation of a carbohydrate into a carbocycle. In this reaction, the stereoselective cyclization of (56), which contains an aldehyde tethered to an activated alkene, produced the polyoxygenated cyclopentane (57), a crucial intermediate in the synthesis. Stereochemistry of the cyclization product (57) was confirmed by the combination of chemical transformations and spectroscopic methods.

We also have developed the first synthetic method that directly converts aldehydes and ketones into 1,2-diacetates, using commercially available reagents bromomethyl acetate, samarium diiodide and HMPA. Since the initial addition product, 1,2-diacetates, are very easy to hydrolyse to 1,2-diols, this reagent combination is also a good hydroxymethyl anion equivalent. Because of the mild reaction conditions and high yields in both addition and the deprotection steps, synthetic chemists should benefit from our method. One can also expect further expansions of our methodology e.g.

different protecting groups, different electrophiles. However; this method can not be used with aromatic aldehydes and ketones where the pinacol formation is very facile. The complete scope and the limitations of this methodology are unknown, however, it should open new research avenues for organic chemists.

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BIOGRAPHICAL SKETCH

Hikmet Satici was born in a small village of Kastamonu, Turkey, on the 5th of November, 1963. He went to primary school (Cevizli Ilkokulu), secondary school (Orhangazi Lisesi), and the high school of commerce (Kartal Ticaret Lisesi) in Istanbul where his parents live. He graduated from high school in 1980 and the same year he joined the Chemistry Department of the Middle East Technical University in Ankara, Turkey. In 1985, he obtained his B.S. in chemistry from METU. He came to the United States in August 1985 and started his graduate studies in chemistry at the University of Florida in Gainesville, Florida.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric J. Enholm, Chairman
Assistant Professor of
Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

James A. Deyrup
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth Wagener
Associate Professor of
Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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December, 1990

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